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Do brain activation changes persist in athletes with a history of multiple concussions who are asymptomatic?

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Abstract

Primary objective: To evaluate brain activation patterns of asymptomatic athletes with a history of two or more concussions.
Research design: A paired case-control design was used to evaluate brain activation patterns during cognitive performance in 14 athletes with a history of two or more concussions and 14 age- and sex-matched controls with no previous concussion.
Methods and procedures: Percentage Blood-Oxygen-Level-Dependent (BOLD) change during an N-back working memory task was assessed in all participants. Performance on the Trail-Making Test Form A and B, Symbol-Digit Modalities Test and the Immediate Post-concussion Assessment and Cognitive Test (ImPACT) was also compared between groups.
Main results: As expected, brain regions activated during the performance of the N-back were equivalent between groups. The groups performed similarly on the neurocognitive measures. The history of concussion group was less accurate than controls on the 1-, 2- and 3-back conditions of the N-back.
Conclusions: Following the complete resolution of symptoms, a history of two or more concussions is not associated with changes in regional brain activation during the performance of working memory task. Compensatory brain activation may only persist during the typically brief time athletes experience symptoms following concussion.

Keywords: *Concussion, functional MRI, neuropsychological*

Introduction

The long-term effects of multiple sports-related concussions remain unclear. In athletes with a history of multiple concussions the increased risk for future concussion [1] and prolonged recovery after each concussive injury [2, 3] is well-documented in the literature. However, studies examining residual neurocognitive impairment and history of concussion are equivocal [1, 4–9]. Collins et al. [6] reported that a history of two or more concussions was associated with lower neurocognitive performance as compared to no previous concussion in collegiate football players. Moser et al. [9] also documented similar cognitive performance between high school athletes with a history of multiple concussions who were asymptomatic for over 6 months and recently (i.e. within 1-week) athletes with concussion who were symptomatic. While these studies support the notion that a history of multiple concussions is associated with long-term decreases in

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neurocognitive function, both Collins et al. [6] and Moser et al. [9] used paper-and-pencil neurocognitive tests in their studies. In contrast, other studies using computerized neurocognitive tests have not documented decreases in neurocognitive performance in athletes with a history of concussion [4, 5, 10, 11]. Researchers have concluded that if long-term effects from multiple concussions exist, neurocognitive testing may not be sensitive enough to detect the long-term subtle changes in neurocognitive function [4].

Recently, functional magnetic resonance imaging (fMRI) has detected changes in regional brain activation between athletes with concussion and non-injured controls in the absence of neurocognitive impairment [12–15]. Athletes with concussion demonstrate brain activations outside regions of interest not observed in non-injured controls, which suggests a compensatory effect following concussion [12, 16, 17]. Evidence of this compensatory regional activation is especially apparent in symptomatic athletes [16, 17]. Chen et al. [16] reported that athletes who are symptomatic with a history of previous concussion exhibited greater activation in temporal and parietal brain regions and less activation in frontal areas compared to non-injured controls on a working memory task. Interestingly, several athletes with concussion were evaluated ~3 months later when asymptomatic. The compensatory regional brain activation patterns initially observed while symptomatic had 'recovered' and became more localized to frontal areas formerly observed in controls. These results not only underscore the importance of symptomology during recovery following concussion, but also provide support for the concept of a neurophysiological recovery following concussion [16].

Other studies report varying degrees of activation within commonly used brain regions (i.e. 'engagement') in mild traumatic brain injury (MTBI) patients. At ~1 month post-injury, McAllister et al. [14, 15] reported varying magnitudes of regional activation within common brain regions, despite similar performance on a working memory task between symptomatic MTBI patients and non-injured controls. This finding suggests an 'engagement' difference such that MTBI patients demonstrated an inability to appropriately allocate resources to meet increased working memory demands [15]. McAllister et al. [15] did not extend their study to examine if these changes persisted following the resolution of symptoms in their sample.

Studies investigating the long-term effects of multiple concussions have failed to produce consistent results, which have been attributed to the lack of sensitivity of measures used to assess cognitive performance. Functional MRI has shown promise in detecting differences in regional brain activation patterns in symptomatic athletes with concussion and MTBI patients, but the efficacy of this measure in detecting the long-term effects of multiple concussions in asymptomatic athletes is under-studied. Moreover, the concept of a 'neurophysiological recovery' from compensatory and engagement brain activation patterns following the symptom resolution warrants additional study, particularly in asymptomatic athletes with a history of multiple concussions who have had time to fully recover from their most recent injury.

The present study investigated the potential long-term effects of two or more concussions in asymptomatic athletes. The primary purpose was to examine regional brain activation patterns elicited during a working memory task. A secondary purpose was to examine differences in behavioural performance on computerized and paper-and-pencil neurocognitive tests between asymptomatic athletes with and without a history of two or more concussions.

Methods

A paired, case-control design was used to compare neurocognitive function, working memory performance and brain activation patterns between asymptomatic athletes with a history of concussion and matched controls.

Participants

A total of 14 asymptomatic athletes with a history of two or more concussions and 14 age- and sex-matched controls without a history of concussion participated in the study. Asymptomatic status was defined using the following criteria: (1) receiving medical clearance from last diagnosed concussion by a sports medicine professional, (2) no medical documentation of concussion, (3) no self-reported recurrence of concussive symptoms for at least 3 months prior to study and (4) presented with no concussion symptoms at the time of study as self-reported on the Post-Concussion Symptom Scale (PCSS) and follow-up verbal symptom checklist by the researcher. The history of concussion group was comprised of 14 collegiate and high school athletes with a reported average of 2.43 (SD = ±0.65) previous concussions and 14 collegiate and high school athlete controls matched on age and sex with no medical documentation of previous concussion. The average time since recovering from their last concussion (i.e. asymptomatic and medical clearance to return to full activity) was ~9 months (SD = ±6.67) (see Table I). Although participants

Table I. Descriptive data on previous concussions for asymptomatic athletes with a history of two or more concussions ($n = 14$).

Athlete	No. of concussions	Time since last concussion (months)
1	2	4
2	2	14
3	3	26
4	2	8
5	2	4
6	2	10
7	3	8
8	2	6
9	2	8
10	2	14
11	3	4
12	3	3
13	2	3
14	4	18

were not matched for education level, the history of concussion group (nine high school, five college) and the control group (eight high school, six college) did not differ significantly on education level ($\chi^2 = 0.15$, $p = 0.70$). Any participant with a history of learning disability, psychiatric disorder, substance abuse, hyperactivity disorder, brain or major neurological injury, anatomical abnormalities and/or migraines were excluded.

Instrumentation

The Immediate Post-Concussion Assessment Cognitive Testing (ImPACT). The ImPACT version 5.0 is a computer-based neurocognitive test battery assessing cognitive function following concussion [18]. Outcome variables for ImPACT include verbal memory, visual memory, reaction time, processing speed and total concussion symptoms from the PCSS. Schatz et al. [19] documented a combined sensitivity of 81.9% for ImPACT indices and total symptom score and a specificity of 89.4%; positive likelihood ratio was ~8:1 and negative likelihood ratio was 2:1.

Trail-Making Test Forms A and B. The Trail-Making Test Forms A and B assess complex visual scanning, motor speed, divided attention and cognitive flexibility and ability to shift strategy [20, 21]. Form A requires participants to connect consecutively numbered circles on a worksheet while Form B requires the participant to connect consecutively numbered circles and letters by alternating between the two sequences.

Symbol Digit Modalities Test. The Symbol Digit Modalities Test [22, 23] is a simple substitution task requiring the participant to use a reference key to pair specific numbers with given geometric figures as fast as possible for 90 seconds. This inverse form of the Digit Symbol Test [24] assesses attention, visual scanning and motor speed.

N-back Working Memory Task. The N-back requires the participant to watch and attempt to remember sets of 12 upper and lowercase letters that appear one at a time on a computer screen. Four conditions (i.e. working memory loads) were used: 0-back, 1-back, 2-back and 3-back. Each of these conditions increased in difficulty from the 0-back to 3-back. This task was similar to the N-back paradigm used by previous researchers [25] and was implemented as a block design that included four 6.15-minute runs during fMRI. Fifteen seconds of fixation preceded the start of the first stimuli block in each run; this data period was discarded. Each of the four runs was counterbalanced and included eight (four repeated conditions) stimuli blocks. Each stimulus block contained 12 letters that appeared one at a time for 500 milliseconds followed by a blank screen that remained for 2000 milliseconds. All stimuli blocks were 30 seconds long, alternating with 15 second fixation periods between them. Targets were pseudo-randomly positioned within and across all runs, blocks and distractor foils (e.g. 1-back targets appearing during the 2-back condition) were 'pseudo-randomly' positioned within and across all four runs.

Functional MRI data pre-processing

The experiment was conducted on a GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. Echo planar images (EPI), starting from the most inferior regions of the brain, were acquired with the following parameters: 36 contiguous 3-mm axial slices in an interleaved order, TR/TE = 2500/27.7 ms, flip angle = 80°, FOV = 220 mm, matrix size = 64 × 64, voxel-size = 3.4375 × 3.4375 × 3 mm, with the first four data points discarded. Each volume of slices were acquired 144 times during each of the four functional runs while participants viewed the stimuli and pressed a pre-designated button to indicate target or non-target, which resulted in a total of 576 volumes of images during the entire experiment. After the functional data acquisition, high-resolution volumetric T_1-weighted spoiled gradient-recalled (SPGR) images with cerebrospinal fluid suppressed were obtained to cover the whole brain with 180 contiguous 1 mm sagittal slices, TR/TE = 8.596/3.828 ms, flip angle = 8°, FOV = 240 mm, matrix

size = 256 × 256. These images were used to register subject functional data to normalized stereotactic space.

Functional MRI and MRI data were pre-processed and analysed using FMRIB's Software Library (FSL) fMRI Expert Analysis Tool (FEAT) [26]. Functional data were brain-extracted [27], motion-corrected to the median functional image using b-spline interpolation (4 df), high-pass filtered (60 s) and spatially smoothed (9 mm full width at half maximum (FWHM), isotropic). The anatomical volume was brain-extracted and registered to the standard space T1 MNI template using tri-linear interpolation with FMRIB's Linear Image Registration Tool (FLIRT, 12 df) [28]. The median functional image was registered to the anatomical volume and then transformed to the MNI template.

First level subject analyses. Statistical images were created using FEAT with an improved General Linear Model (GLM). Regressors were created by convolving blocked time-course files for each condition with a canonical HRF. Time-course files were generated separately for each of four working memory loads (0-back, 1-back, 2-back, 3-back). Each regressor was entered into the GLM along with their temporal derivative and six rigid body movement parameters (motion in x, y, z, roll, pitch and yaw directions) which were modelled as nuisance covariates.

Group analyses. Statistical maps were entered into a 2 group (history of concussion, control) × 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVA. Paired samples t-test contrasts for within and between effects were performed in a second-level GLM. For all within-subjects comparisons individual subject beta-images were entered along with a regressor per subject to account for subject-specific variance. Group analyses were performed using FSL's FLAME higher-level analysis tool [29] and all F- and t-statistics were converted to unit-normal z-statistics.

Functional ROI analyses. Functional ROIs were defined by clusters surviving voxel-wise thresholding at FWE-corrected $p < 0.05$ with a minimum extent of 10 contiguous voxels. Percentage signal-change values were extracted from individual subject beta-maps within ROIs functionally defined by the second level contrast results, group-averaged and subjected to offline analysis.

Procedures

This study was approved by the university's Institutional Review Board. Participants were asked to self-report and recall any diagnosed concussions or concussive events that occurred in the previous 3 months to help determine asymptomatic status. A detailed intake form was used to provide examples of concussive events (e.g. car accident, impacts to the head, whiplash). All participants then completed ImPACT [30] including the PCSS, Trail-Making Test Form A and B [20] and the Symbol Digit Modalities Test [23] in this order. Functional MRI was scheduled within 1 week of completing the neurocognitive battery. Confirmatory verbal follow-up assessment of symptoms referencing the PCSS checklist was conducted by the researcher with each participant. All participants completed the N-back working memory task [31, 32] during fMRI.

Data analysis

Neurocognitive performance. Between-groups independent samples t-tests were conducted for each ImPACT composite score, total symptoms and completion time (seconds) on the Form A and B of the Trail-Making Test and the Symbol Digit Modalities Test.

N-Back Working Memory Task. Separate 2 group (concussion history, no concussion history) × 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVAs for reaction time (milliseconds) and accuracy (percentage correct) were performed. Statistical significance was set at $p \leq 0.05$. A post-hoc diffusion model was also applied to examine N-back data for speed-accuracy trade-off [33].

fMRI data analysis. A whole-brain 2 group × 4 working memory load repeated measures ANOVA was performed to identify any brain regions that interacted between groups and working memory load. In addition, a more sensitive functional ROI mask (Family-Wise Error: FWE corrected $p < 0.05$) was derived by using 3-back > 0-back contrast from controls. Percentage signal-change was then extracted from these regions in both groups (all subjects) and tested using a series of 2 (group) × 4 (working memory load) repeated measures ANOVAs for each brain region using SPSS at a more liberal significance threshold of uncorrected $p < 0.05$. In order to ensure that the functional ROI localization based on the control group was unbiased, a functional ROI mask (FWE-corrected, $p < 0.05$) using the 3-back > 0-back contrast was derived from the history of concussion group and

Table II. Results from a series of independent samples *t*-tests conducted on neurocognitive scores.

	History of concussion		Controls		
	M	SD	*M*	SD	*p*
Verbal Memory	0.89	±0.10	0.89	±0.10	0.88
Visual Memory	0.83	±0.09	0.86	±0.08	0.34
Motor Processing Speed	43.27	±6.41	43.13	±5.60	0.95
Reaction Time	0.53	±0.07	0.54	±0.05	0.77
Total Symptoms	0.00	0.00	0.29	±0.73	0.15
Trail-Making Test Form A	16.86	±2.31	15.37	±3.45	0.19
Trail-Making Test Form B	38.45	±12.18	35.96	±7.99	0.53
Symbol Digit Modalities Test	62.86	±13.25	60.14	±6.64	0.50

percentage signal-change was extracted from these regions in both groups and tested using SPSS. A Bonferroni correction was used in the preceding analyses to control Type I error due to multiple ANOVAs being conducted on the ROIs. Additional exploratory analyses included between-group whole-brain independent *t*-tests conducted for each working memory load and whole-brain paired *t*-tests conducted on the 1-back > 0-back; 2-back > 1-back; and 3-back > 2-back contrasts.

Results

Neurocognitive and behavioural performance

No significant differences existed between groups on any of the neurocognitive measures or total symptoms (see Table II). Reaction time for correct targets on the N-back was similar between groups at each working memory load ($F[3, 24] = 0.25$, $p = 0.86$, $\eta^2 = 0.03$). However, controls were more accurate than the history of concussion group ($F[1, 26] = 14.92$, $p = 0.001$, $\eta^2 = 0.37$) on the 1-back ($p = 0.01$), 2-back ($p = 0.04$), and 3-back ($p = 0.02$) conditions (see Figure 1). There was no evidence of a speed-accuracy trade-off difference between groups as measured by diffusion modelling of the response-time and accuracy data [33], suggesting the observed difference in accuracy was not due to general task difficulty or time pressure.

fMRI results from whole-brain 2 × 4 repeated measures ANOVA

The whole-brain 2 group × 4 working memory load repeated measures ANOVA revealed no significant interaction between group and working memory load or main effect for group. There was a within-subjects main effect for working memory load. Post-hoc whole-brain paired *t*-tests for all athletes were conducted for activation (i.e. 3-back > 0-back) contrasts to further identify which brain regions demonstrated an increase or decrease in response to working memory load. Brain regions of activation were found in the right inferior parietal lobe (R IPL), left middle frontal gyrus (L MFG), right inferior frontal gyrus (R IFG), left inferior frontal gyrus (L IFG), anterior cingulate cortex (ACC), right middle frontal gyrus (R MFG), left inferior parietal lobe (L IPL), precuneus and cerebellum.

Results from functional ROI analyses

Functional ROI analyses derived from control and history of concussion 3-back > 0-back activation contrasts. Between-group differences in BOLD percentage signal change were assessed in 12 brain regions derived from the control group ROIs and 11 brain regions from the history of concussion group ROIs (see Tables III and IV). A Bonferroni-corrected level of significance ($p \leq 0.004$) was used to identify statistical significance.

Results from the repeated measures ANOVAs for the 12 brain regions derived from the control group did not reveal any significant interactions between group and load-level. There was a significant within-subjects effect for working memory load in every brain region, but no main-effect of group. While the concussed group tended to show less activation in the L MFG region derived from the control set of ROIs, the result did not survive a multiple-comparison correction. The results from the repeated measures ANOVAs for the 11 brain regions derived from the history of concussion group did not reveal any significant interactions between group and load-level. There was a significant within-subjects effect for working memory load in every brain region but no main-effect of group. Both functional masks were qualitatively examined for degree of overlap (see Figure 2).

Results from whole-brain independent t-tests

Between-group comparison at each working memory load. There were no significant differences between groups in brain activation at any working

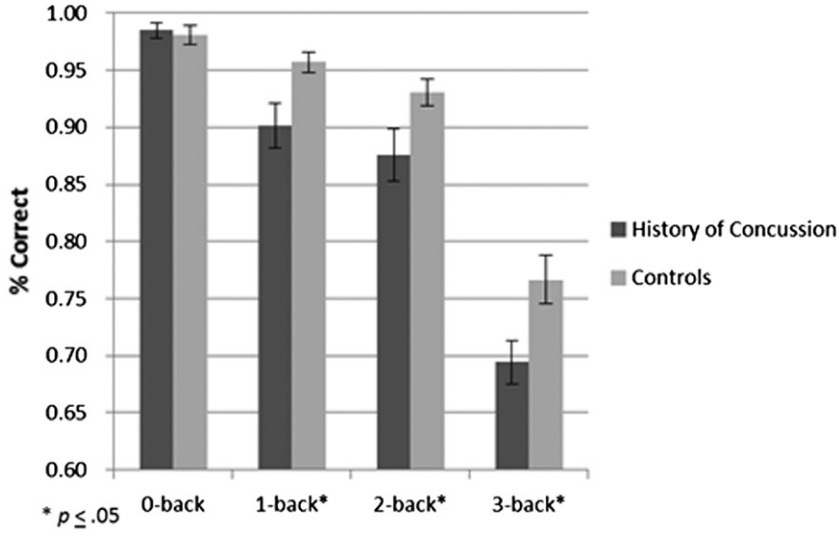

Figure 1. Mean accuracy (percent correct) and standard deviations for N-back working memory performance between asymptomatic athletes with a history of two or more concussions ($n = 14$) and controls ($n = 14$).

Table III. Locations of peak activations in brain regions from the 3-back > 0-back contrast derived from controls ($n = 14$).

				MNI co-ordinates		
Brain region	Brodmann area	# Voxels	*Z*-max	*x*	*y*	*z*
1. R IPL	19, 40	490	9.81	34	−72	46
2. ACC/SMA	8, 32	374	12.4	4	24	42
3. R MFG (R DLPFC)	6, 8	299	12.2	28	14	52
4. R MFG	8	135	10.7	48	32	26
5. L MFG (L DLPFC)	8	112	9.51	−26	4	50
6. R MFG	46	95	8.02	38	44	16
7. Angular Gyrus	19, 39	90	8.43	−32	−62	38
8. L MFG	10	32	7.55	−34	58	−2
9. L IFG	44	30	7.92	−38	8	22
10. Cerebellum		24	7.02	38	−58	−34
11. L IFG	44, 46	19	7.36	−54	18	26
12. L Precuneus	7	11	6.45	−6	−70	44

Table IV. Locations of peak activations in brain regions from the 3-back > 0-back contrast derived from asymptomatic athletes with a history of two or more concussions ($n = 14$).

				MNI co-ordinates		
Brain region	Brodmann area	# Voxels	*Z*-max	*x*	*y*	*z*
1. R IPL (SMG)	40	875	10.4	36	−60	38
2. R MFG (R DLPFC)	46	458	8.07	48	32	24
3. R MFG	10	245	6.53	38	50	0
4. R IFG	47	231	6.45	38	22	−6
5. ACC/SMA	8, 32	165	5.88	10	28	40
6. L MFG	10	140	5.66	−32	52	4
7. L IPL	19, 40	115	5.41	−36	−68	42
8. R Precuneus	7	59	4.78	−8	−72	46
9. L IFG	47	21	4.23	−32	24	−6
10. L MFG (L DLPFC)	9	13	4.07	−18	10	46
11. R MFG	9	12	4.05	24	2	46

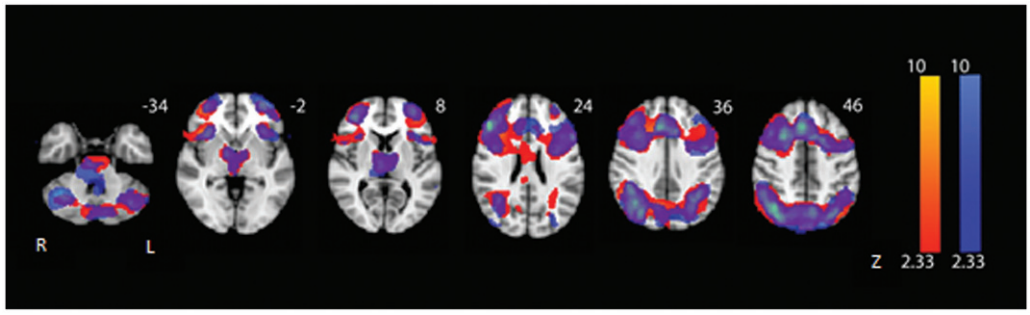

Figure 2. Overlap of both history of concussion (Red) and control groups (Blue) Functional ROI masks at a liberal threshold ($p < 0.01$, uncorrected).

memory load. Further exploration of the data was conducted by examining between-group differences (i.e. whole-brain independent *t*-tests) for the following working memory contrasts: 1-back > 0-back; 2-back > 1-back; and 3-back > 2-back. These comparisons did not reveal any significant findings as both groups showed similar activation in common brain regions at each working memory load.

Discussion

Following the resolution of symptoms, athletes with a history of two or more concussions did not demonstrate compensatory changes or engagement differences in regional brain activation patterns compared to athletes without previous concussion. These fMRI data support the concept of a neurophysiological recovery in asymptomatic athletes with a history of two or more concussions. These athletes also did not differ from those without previous concussion on either paper-and-pencil or computerized neurocognitive tests. Despite similar performance between groups on neurocognitive measures, the history of concussion group was less accurate on the 1-, 2- and 3-back conditions of the N-back. This finding should be interpreted cautiously due to the small sample size employed in this study and warrants additional study.

Relevant to increases in working memory load, asymptomatic athletes with a history of two or more concussions activated the same brain regions as controls. Therefore, the compensation brain activation patterns documented in symptomatic athletes [16, 17] were not found in the present sample. This 'non-significant' finding is important as it supports the notion of a 'neurophysiological recovery' following concussion. This 'recovery effect' was also found by Chen et al. [16], who reported similar task-related activation patterns between controls and athletes with a history of concussion who recently experienced a resolution of symptoms. Chen et al. [16] documented this 'recovery' effect at ~9 months post-concussion, which is the same time period used in the present study. Moreover, the brain regions used by both the 'recovered' (i.e. asymptomatic) athletes and controls in Chen et al. [16] included the same brain regions observed in the present study.

The fMRI findings from the present study suggest that asymptomatic athletes with a history of two or more concussions and controls use similar brain regions in a similar manner. These results do not support the engagement differences previously reported by McAllister et al. [14, 15]. However, a non-significant trend was found in the L MFG at the high working memory load for the history of concussion group compared to controls. Although controls showed increased activation in this brain region at every working memory load, the history of concussion group did not activate this brain region when progressing from the moderate to the high working memory load. This disparity in activation was not found in any whole-brain analysis and was not replicated when using the history of concussion group contrast mask, which may indicate that this finding is spurious.

Similar performances demonstrated by both groups on the paper-and-pencil neurocognitive tests are in contrast to previous studies that have suggested that a history of multiple concussions is associated with prolonged declines in neurocognitive function [6, 8, 9, 34]. The contrast between the current and the aforementioned studies may be due to differences in sample selection criteria (e.g. symptomology, time since last concussion). In the current study all athletes were asymptomatic and recovered from their last diagnosed concussion for ~9 months. Even though athletes were symptomatic, Moser and colleagues [8, 9] required their history of concussion group to be without concussion for at least 6 months, whereas Collins et al. [6] did not report time since last concussion. Differences in these time periods could allow for further resolution

of any lasting cognitive deficits and explain discrepancies between results.

The similar performance between groups on the computerized neurocognitive test is in concordance with other studies using similar computerized measures [2, 4, 5, 10, 11, 35]. Covassin et al. [2] and Iverson et al. [10] reported similar baseline performance on ImPACT between athletes with and without a history of multiple concussions and these data have also been documented for other computerized neurocognitive tests that include the CRI [4, 35] and CogSport [11]. However, none of these studies reported information on symptoms or time since last concussion, which limits direct comparison to the current study's results.

In contrast to the similar performances on the neurocognitive test battery, asymptomatic athletes with a history of two or more concussions identified fewer correct targets than controls on the N-back. This singular finding was anomalous with the fMRI and neurocognitive test results and is not supported in the literature. However, this finding provides tentative evidence of working memory impairment in the history of concussion group, in spite of the lack of corresponding findings regarding brain activation patterns. Subtle dysfunctions of brain activation may not have been detected with the fMRI techniques used in the present study and/or due to low statistical power. Previous fMRI studies conducted with symptomatic athletes with a history of multiple concussions documented no differences in N-back accuracy [12, 16, 17]. Nonetheless, cognitive paradigms such as the N-back may augment neurocognitive assessment that is commonly used for concussion management and additional research is warranted.

There are several limitations in the present study as it employed a small, non-random sample which affects external validity. Variability in time since injury within the concussion history group may have affected their performance. Moreover, the formation of groups was based on self-report of previous concussions and controls may have previously sustained an undiagnosed/undetected concussion. Finally, the present study grouped the actual number of previous concussions into one group. Previous studies have reported more of a cumulative effect for three or more concussions than two or more [6].

Conclusions

In conclusion, following the complete resolution of symptoms a history of two or more concussions is not associated with changes in regional brain activation during the performance of working memory task. Possible changes in activation in the LMFG should be explored further by researchers. Moreover the use of additional cognitive tests such as the N-back may augment current assessments used for concussion management.

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